US005547994A

United States Patent [19]

Barbierich et al.

[11] Patent Number: 5,547,994

[45] Date of Patent: Aug. 20, 1996

[54] METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(−) ALBUTEROL

[75] Inventors: Timothy J. Barbierich, Concord; James W. Young, Still River, both of Mass.

[73] Assignee: Sepracor, Inc., Marlborough, Mass.

[21] Appl. No.: 335,180

[22] Filed: Nov. 7, 1994

Related U.S. Application Data

[63] Continuation of Ser. No. 163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] Int. Cl.[6] A61K 31/135

[52] U.S. Cl. 514/649; 514/826

[58] Field of Search 514/649, 826

[56] References Cited

U.S. PATENT DOCUMENTS

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FOREIGN PATENT DOCUMENTS

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Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Hesslin & Rothenberg, P.C.

[57] ABSTRACT

The optically pure R(−) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(−) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

6 Claims, No Drawings

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(−) ALBUTEROL

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 08/163,581, filed Dec. 7, 1993 and now U.S. Pat. No. 5,362,755, which was a continuation of application Ser. No. 07/896,725, filed Jun. 9, 1992, now abandoned, which was a continuation of application Ser. No. 07/461,262 filed Jan. 5, 1990, now abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, dizziness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the bronchodilation activity of the R(−) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual to whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1 [(tert-butylamino) methyl] -4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a par-

ticular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalant form can include, in addition to the drug(s), a liquid carrier and/or propellant. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of treating an acute attack of asthma, while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to an individual suffering from an acute attack of asthma a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method of claim 1 wherein the amount of the R(−) isomer of albuterol is greater than approximately 90% by weight.

3. A method of claim 2 wherein the amount of the R(−) isomer of albuterol is greater than 99% by weight.

4. A method of claim 1 comprising administering to the individual by inhalation from approximately 30 mcg to approximately 90 mcg of the R(−) isomer of albuterol per dose.

5. A method of treating an acute attack of asthma, while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to an individual suffering from an acute attack of asthma a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, and at least one additional drug selected from the group consisting of bronchodilators, antihistamines and analgesics.

6. A method of claim 5 wherein the analgesic is selected from the group consisting of aspirin, acetaminophen and ibuprofen.

* * * * *

GP1205

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Barberich *et al.* Docket No.: 0701.027D

Serial No.: 08/691,604 Group Art Unit: 1205

Filed: August 15, 1996 Examiner: Henley III, R.

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

#10/13
3RP
12/12/97

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Box Non Fee Amendment, Washington, D.C. 20231, on November 20, 1997.

Philip E. Hansen
Agent for Applicants
Reg. No. 32,700

Date of Signature: November 20, 1997

DEC

Assistant Commissioner for Patents
Box Non Fee Amendment
Washington, D.C. 20231

AMENDMENT AND RESPONSE UNDER 37 C.F.R. 1.111

Dear Sir:

This is a response to an Office Action mailed August 25, 1997 (paper number 9). As response to the Action is due by November 25, 1997, this paper is timely filed.

Amendment

Please amend the application as follows:

In the claims:

Please cancel claims 13 and 14.

Line 1 of claims 15, 16, 17 and 19, delete "13 or 14" and insert therefor --23--.

Response

The present application is a continuation of USSN 08/335,480, which included claims 1-12. All claims pending in the original application were canceled and new claims 13-23 were added in a preliminary amendment filed with the present application. Claims 13 and 14 are canceled herein; claims 15-23 are pending in this continuation application.

Statutory Double Patenting Rejection

Claim 13 was rejected as claiming the same invention as that of claim 1 of prior U.S. Patent No. 5,547,994 and claim 14 was rejected as claiming the same invention of claim 1 of prior U.S. Patent No. 5, 362,755. To overcome this rejection, both claim 13 and claim 14 have been canceled by amendment above.

Obvious-type Non-Statutory Double Patenting Rejection

Claims 13 and 15-22 were rejected as being unpatentable over claims 1-4 of prior U.S. Patent No. 5,547,994. Claims 14 and 15-22 were rejected as being unpatentable over claims 1-5 of prior U.S. Patent No. 5,362,755. Claim 23 was rejected as being unpatentable over claim 1 of prior U.S. Patent No. 5,547,994 and claim 1 of prior U.S. Patent No. 5,362,755.

In response to the above rejections, Applicants herewith submit Terminal Disclaimers in accordance with 37 CFR 1.321 (b) and (c) and fee under 37 C.F.R. 1.20(d).

Disclosure of Information under 37 CFR §1.56

In the prosecution of parent case 08/335,480 (now US patent 5,547,994), applicants presented a Declaration under 37 CFR §1.132 by John R. McCullough. Dr. McCullough presented results of tests on airway smooth muscle cells that demonstrated unexpected differences among the enantiomers and racemate of albuterol on calcium mobilization and on

airways hyperreactivity. Following the presentation of this declaration and the accompanying response on January 22, 1996, the claims were allowed. Earlier in prosecution, on June 6, 1995, applicants had presented a Declaration under 37 CFR §1.132 by Dean A. Handley showing the tremorogenicity of the enantiomers in mice. From the results in mice, Dr. Handley concluded that the use of the pure R enantiomer would result in less potential for tremorogenicity in humans. In the next Office Action following that declaration, the Examiner maintained the rejection and noted that the Handley declaration had been carefully considered, but it did not persuade the Examiner of error in his earlier rejection.

Subsequent to the prosecution of the '480 case, applicants have undertaken clinical trials in preparation for bringing the compositions and methods of the invention onto the market, including clinical trials directed toward determining tremorogenicity in humans. The results of the studies indicate that, notwithstanding the effects seen in the mouse tremorogenicity study, the S enantiomer does not appear to be tremorogenic in humans. Applicants therefore do not believe it would be proper to rely on the declaration of Dr. Handley for patentability. Applicants present this information in order to satisfy their duty of disclosure, but they believe it has no practical effect on the patentability *vel non* of the claims, since the Examiner did not rely on the declaration of Dr. Handley for his determination of allowability. As regards the findings in the declaration of Dr. McCullough, on which the Examiner appears to have relied for allowance, Dr. McCullough remains comfortable with the results and conclusions presented in that declaration.

There being no further outstanding issues, the application is believed in condition for allowance and such action is respectfully requested. However, should the Examiner have any further questions or comments regarding the pending claims, he is urged to contact Applicant's representative at the number below.

Respectfully submitted,

Philip E. Hansen
Agent for Applicants
Reg. No. 32,700

Dated: November 20, 1997

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Albany, New York 12203
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Terminal Disclaimer To Obviate A Double Patenting Rejection Over A Prior Patent	Docket No. 0701.027D

In Re Application Of: Barberich et al.

Serial No.	Filing Date	Examiner	Group Art Unit
08/691,604	08/15/96	Henley III, R.	1205

Invention: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)-ALBUTEROL

Owner of Record: SEPRACOR, INC.

TO THE ASSISTANT COMMISSIONER FOR PATENTS:

The above-identified owner of record of a 100% percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior Patent No. 5,362,755 . The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors and/or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it later expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of an organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney of record.

Philip E. Hansen — Dated: November 20, 1997
Signature

Philip E. Hansen
Typed or Printed Name

☒ Terminal disclaimer fee under 37 C.F.R. 1.20(d) included.
☒ PTO suggested wording for terminal disclaimer was unchanged.
☐ Certification under 37 C.F.R. 3.73(b) is required if terminal disclaimer is signed by the assignee.

12/26/1997 LSHEID 00000010 08691604
01 FC:144 110.00 OP

P32/REV01

Terminal Disclaimer To Obviate A Double Patenting Rejection Over A Prior Patent

Docket No. 0701.027D

In Re Application Of: Barberich et al.

Serial No.	Filing Date	Examiner	Group Art Unit
08/691,604	08/15/96	Henley III, R.	1205

Invention: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)-ALBUTEROL

Owner of Record: SEPRACOR, INC.

TO THE ASSISTANT COMMISSIONER FOR PATENTS:

The above-identified owner of record of a 100% percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior Patent No. 5,547,994. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors and/or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it later expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

☐ For submissions on behalf of an organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

☒ The undersigned is an attorney of record.

Philip E. Hansen Dated: November 20, 1997

Signature

Philip E. Hansen

Typed or Printed Name

☒ Terminal disclaimer fee under 37 C.F.R. 1.20(d) included.

☒ PTO suggested wording for terminal disclaimer was unchanged.

Certification under 37 C.F.R. 3.73(b) is required if terminal disclaimer is signed by the assignee.

PS2/REV01

SUBJECT: DECISION ON TERMINAL DISCLAIMERS INFORMAL FORM

DATE: 12-15-97 APPL. S.N.: 08/691,684

TO EXAMINER: R. Hendricks ART UNIT: 1205

M. Montgomery ROOM 6618 MAILROOM DATE 11-24-97

AFTER FINAL YES ___ NO ___ NUMBER OF T.D(S). FILED ___

INSTRUCTIONS: I have reviewed the submitted T.D. with the results as set forth below. If you agree, please use the appropriate form paragraphs identified by this informal memo in your next office action to notify applicant about the T.D. If you disagree with my analysis or have questions at all about the acceptability of the T.D., please see me or our Special Program Examiner. [illegible] INTERNAL MEMO ONLY. IT MUST NOT BE MAILED TO APPLICANT NOR SHOULD A COPY BE LEFT IN FILE.

[X] The T.D. is PROPER and has been recorded. (See 14.23).

[ ] The T.D. is NOT PROPER and has not been accepted for the reason(s) checked below. (See 14.24).

[ ] The recording fee of $_____ has not been submitted nor is there any pre authorization in the application file to charge to a deposit account. (See 14.26.07)

[ ] Application Examiner has not processed T.D. fee. (See fee authorization).

[ ] The T.D. does not satisfy Rule 321(b)(3) in that the person who has signed the T.D. has not stated his/her interest (and/or the extent of the interest of the business entity represented by the signature) in the application/patent. (See 14.26 and 14.26.01).

[ ] The T.D. lacks the enforceable only during the common ownership clause needed to overcome a double patenting rejection, Rule 321(c). (See 14.27, 14.27.01).

[ ] It is directed to a particular claims(s), which is not acceptable since "the disclaimer must be of a terminal portion of the term of the entire patent to be granted". MPEP 1490. (See 14.26, 14.26.02).

[ ] The person who signed the terminal disclaimer:
- [ ] has failed to state his/her capacity to sign for the business entity, (See 14.28).
- [ ] is not recognized as an officer of the assignee. (See 14.29 and possibly 14.29.01).

[ ] No documentary evidence of a chain of title from the original inventor(s) to assignee has been submitted, nor is the reel and frame specified as to where such evidence is recorded in the office. 37 CFR 3.73(b). (See 1140 O.G. 72). NOTE: This documentary evidence or the specifying of the reel and frame may be found in the T.D. or in a seperate paper submitted by applicant. (See 14.30).

[ ] No "statement" specifying that the evidentiary documents have been reviewed and that, to the best of the assignee's knowledge and belief the title is in the assignee seeking to take action, 37 CFR 3.73(b). (See 1140 O.G. 72) (See 14.31).

[ ] The T.D. is not signed. (See 14.26, 14.26.3), or 14.26.03 if TD is not signed by all the owners.

[ ] Attorney not of record in oath/decl. or a seperate paper filed appointing a new or associate attorney. (See 14.29.01).

[ ] The serial number of the application (or the number of the patent) which forms the basis for the double patenting is missing or incorrect. (See 14.32).

[ ] The serial number of this application (or the number of the patent in reexam or reissue case(s) being disclaimed is missing or incorrect. (See 14.26, 14.26.04 or 14.26.05).

[ ] The period disclaimed is incorrect or not specified. (See 14.27, 14.27.2 or 14.27.3)(For Samples 14.27.04 and 14.27.05)

[ ] Other: _____

[ ] Suggestion to request refund of $ _____. (See 14.35, 14.36).

[ ] EXAMINER NOTE: IF APPLICATION IS IN CONDITION FOR ALLOWANCE ANY OF THE ABOVE INFORMALTIES MAY BE FAXED IN TO THE GROUP

FOR SAMPLE TERMINAL DISCLAIMERS AND CERTIFICATES:

[ ] Sample of a TD over a pending application and assignee Certificate (See 14.37).
[ ] Sample of a TD over a prior patent and assignee Certificate (See 14.38).
[ ] Sample Assignee Certificate under 37 CFR 3.73 (b) (See 14.39)

Notice of Allowability	Application No. 08/891,604	Applicant(s) Timothy L. Barberich et al.
	Examiner Ray Henley	Group Art Unit 1205

laims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included with (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be s in due course.

his communication is responsive to *the amendment and terminal disclaimer filed November 24, 1997*.

he allowed claim(s) is/are *15-23*.

he drawings filed on _____ are acceptable.

cknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*rtified copies not received: _____.

cknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

ORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE MONTHS FROM THE "DATE MAILED" of this Office action. Failure to timely comply will result in DONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

e the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses t the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

plicant MUST submit NEW FORMAL DRAWINGS

because the originally filed drawings were declared by applicant to be informal.

ncluding changes required by the Notice of Draftsperson's Patent Drawing Review, PTO-948, attached hereto or o Paper No. _____.

ncluding changes required by the proposed drawing correction filed on _____, which has been pproved by the examiner.

ncluding changes required by the attached Examiner's Amendment/Comment.

ntifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the reverse side of the wings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official spperson.

the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

sponse to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES ERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER E of the NOTICE OF ALLOWANCE should also be included.

hment(s)

Notice of References Cited, PTO-892

formation Disclosure Statement(s), PTO-1449, Paper No(s). _____

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

terview Summary, PTO-413

aminer's Amendment/Comment

aminer's Comment Regarding Requirement for Deposit of Biological Material

aminer's Statement of Reasons for Allowance

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12M2/1217

PHILIP E. HANSEN
HESLIN AND ROTHENBERG
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ALBANY NY 12203

...LICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT		DATE MAILED
08/691,604	08/15/96	009	HENLEY III, R	1205	12/17/97

BARBERICH, TIMOTHY L.

...ETHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

...S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
0701.027D	514-649.000	V41	UTILITY	YES	$660.00	03/17/98

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APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT		DATE MAILED
08/691,604	08/15/96	009	HENLEY III, R	1205	12/17/97

...Named ...licant: BARBERICH, TIMOTHY L.

...TITLE: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
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08/691,604	5760090	1614	9200 4 0012 011 05

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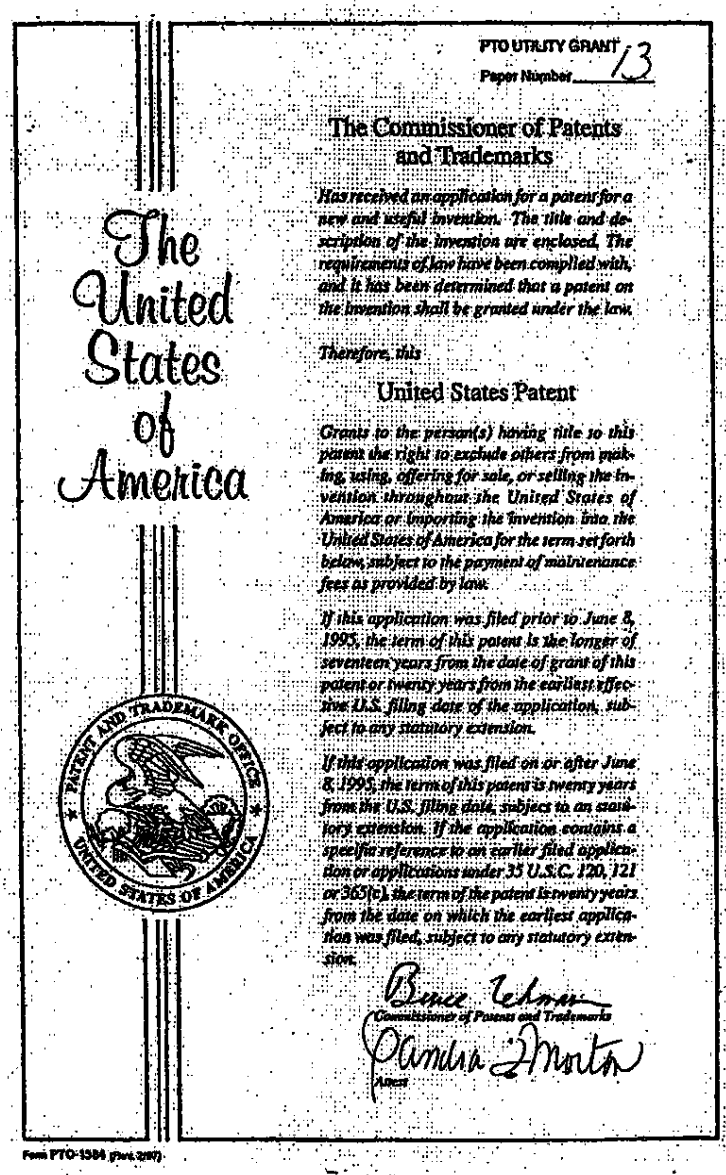

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(19) BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENTAMT

Patentschrift

(11) DE 2128258 C2

(51) Int. Cl.:
C 07 C 91/34
A 61 K 31/135

(21) Aktenzeichen: P 21 28 258.6-42
(22) Anmeldetag: 7. 6. 71
(43) Offenlegungstag: 23. 12. 71
(45) Veröffentlichungstag der Patenterteilung: 11. 8. 83

Innerhalb von 3 Monaten nach Veröffentlichung der Erteilung kann Einspruch erhoben werden

(30) Unionspriorität: (32) (33) (31)
17.06.70 GB 29367-70

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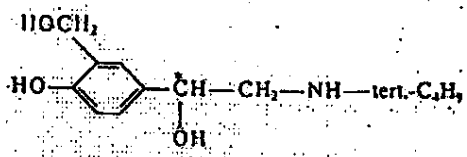
(56) Im Prüfungsverfahren entgegengehaltene Druckschriften nach § 44 PatG:
FR 15 57 677

(54) Verfahren zur Herstellung der optischen Enantiomeren von α¹-tert.-Butylaminomethyl-4-hydroxy-m-xylen-α¹,α³-diol, das R(-)-Enantiomere in Form des Hydrogenacetat-monomethanol-Solvats und Arzneimittel

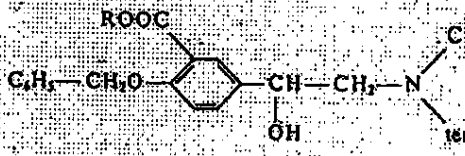
Patentansprüche:

1. Verfahren zur Herstellung der optischen Enantiomeren von α^1-tert.-Butylaminomethyl-4-hydroxy-m-xylylen-α^1,α^3-diol der Formel I



(I)

und ihrer Salze mit Säuren, dadurch gekennzeichnet, daß man einen basischen Ester der allgemeinen Formel II



(II)

in der R einen unverzweigten oder verzweigten Alkylrest mit 1 bis 6 Kohlenstoffatomen bedeutet, mit einer optisch aktiven Form der Di-p-toluylweinsäure in einem organischen Lösungsmittel umsetzt, das entstandene Salz fraktioniert kristallisiert und die diastomeren Salze auftrennt, hieraus in üblicher Weise die Base in Freiheit setzt und diese in beliebiger Reihenfolge reduziert und katalytisch entbenzyliert und gegebenenfalls die erhaltene Verbindung mit einer anorganischen oder organischen Säure in ein Salz überführt.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß man die Umsetzung mit der optisch aktiven Form der Di-p-toluylweinsäure in einem Carbonsäureester als Lösungsmittel durchführt.

3. Verfahren nach Anspruch 1 und 2, dadurch gekennzeichnet, daß man die Reduktion mit Lithiumaluminiumhydrid durchführt und zur katalytischen Entbenzylierung einen Palladium-auf-Holzkohle-Katalysator verwendet.

4. Verfahren nach Anspruch 1 bis 3, dadurch gekennzeichnet, daß man das Verfahren, ausgehend von dem dl-Racemat des 5-(2-Benzyl-tert.-butylamino-1-hydroxyäthyl)-2-benzyloxybenzoesäuremethylesters als basischem Ester der allgemeinen Formel II, durchführt.

5. R(−)-Enantiomer von α^1-tert.-Butylaminoäthyl-4-hydroxy-m-xylylen-α^1,α^3-diol-hydrogenacetat-monomethanol-Solvat.

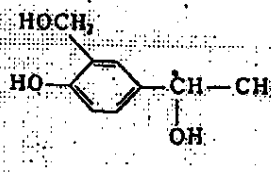
6. Arzneimittel, enthaltend das gemäß Anspruch 1 bis 4 hergestellte R(−)-Enantiomere oder dessen Säureadditionssalze oder die Verbindung gemäß Anspruch 5, als Wirkstoff.

Aus der FR-PS 15 57 677 sind Phenylaminoäthanol-Derivate, wie α^1-tert.-Butylaminomethyl-4-hydroxy-m-xylylen-α^1,α^3-diol, bekannt. Diese Verbindungen können die β-Rezeptoren der adrenergenen Nerven stimulieren. Diese Phenylaminoäthanol-Derivate können theoretisch in zwei optisch isomeren Formen vorliegen. Ebenso wie in Beispiel 16 der FR-PS 15 57 677 ist bisher nur die Racematform der vorstehend genannten Verbindung beschrieben worden.

Aufgabe der Erfindung war es daher, ein Verfahren zur Herstellung der optisch aktiven isomeren Formen (Enantiomeren) von α^1-tert.-Butylaminomethyl-4-hydroxy-m-xylylen-α^1,α^3-diol in möglichst reiner Form bereitzustellen. Diese Aufgabe wird durch die Erfindung gemäß den Patentansprüchen 1 bis 4 gelöst.

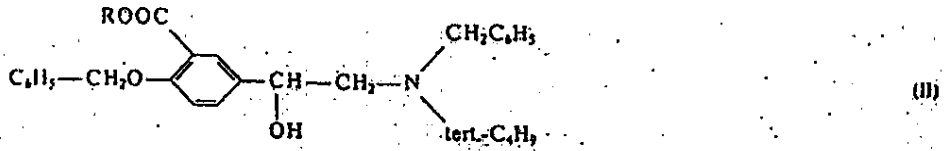
Weitere Gegenstände der Erfindung sind das R(−)-Enantiomere des α-tert.-Butylaminomethyl-4-hydroxy-m-xylylen-α^1,α^3-diol-4-hydrogenacetat-monomethanol-Solvats gemäß Anspruch 5 sowie Arzneimittel auf der Basis des durch das erfindungsgemäße Verfahren erhältlichen R(−)-Enantiomeren oder dessen Säureadditionssalzen oder des Hydrogenacetat-monomethanol-Solvats des vorgenannten Diols, entsprechend Anspruch 6.

Das erfindungsgemäße Verfahren zur Herstellung der optischen Enantiomeren von α^1-tert.-Butylaminomethyl-4-hydroxy-m-xylylen-α^1,α^3-diol der Formel I



(I)

ü ihrer pharmakologisch verträglich[illegible] Salze mit Säuren ist dadurch gekennzeichnet, daß man einen basischen ster der allgemeinen Formel II



(II)

der R einen unverzweigten oder verzweigten kylrest mit 1 bis 6 Kohlenstoffatomen bedeutet, mit er optisch aktiven Form der Di-p-toluylweinsäure in em organischen Lösungsmittel umsetzt, das entstan- ne Salz fraktioniert kristallisiert und die diastomeren lze auftrennt, hieraus in üblicher Weise die Base in reiheit setzt und diese in beliebiger Reihenfolge duziert und katalytisch entbenzyliert und gegebenen- lls die erhaltene Verbindung mit einer anorganischen ure in ein Salz überführt.

Die erfindungsgemäße Gewinnung der optischen antiomeren unterscheidet sich von der in der FR-PS 57 677 angesprochenen üblichen Racematspaltung durch, daß nicht das als Endprodukt gewünschte Diol ner Trennbehandlung unterworfen wird, sondern eine rstufe in Form des basischen Esters gemäß Formel II. Auf diese Weise lassen sich die betreffenden antiomeren in sehr reiner Form gewinnen, was bisher cht möglich war.

Diese Reinheit und die hohe pharmakologische ktivität, speziell des R(−)-Isomeren sind besonders rtvoll für den Einsatz als Wirkstoff in Arzneimitteln.

Die Reduktion wird z. B. mit einem Metallhydrid oder komplexen Metallhydrid durchgeführt. Die Entbenzylie- ung wird durch hydrierende Spaltung in Gegenwart nes Edelmetallkatalysators, wie Palladium, durchge- führt. Das Produkt kann als Salz mit einer Säure isoliert werden.

Die Isomeren haben in der Form des Acetat-Mono- ethanolats folgende physikalische Eigenschaften:

	Smp. °C	$[\alpha]_D^{25}$	c(CH_3OH)
R(−)-Isomer	143,9	−36,9°	0,27
S(+)-Isomer	143,0	+36,9°	0,23

Die reinen Isomeren er Formel I haben folgende Eigenschaften:

R(−)-Isomer	−26,0°	0,36
S(+)-Isomer	+25°	0,4

Die Salze können sich von organischen oder anorganischen Säuren ableiten, wie Maleinsäure, Fumarsäure, Äpfelsäure, Bernsteinsäure, Essigsäure, Weinsäure, Salzsäure, Schwefelsäure und Phosphorsäure.

Das R(−)-Isomer der Verbindung der Formel I wirkt als Antagonist der erhöhten Bronchialresistenz, die durch Verabfolgen von Acetylcholin an anästhesierte Meerschweinchen erzeugt wird (Konzert-Rössler-Präparat).

Daher betrifft die Erfindung auch Arzneimittel entsprechend der oben gegebenen Definition, welche gegebenenfalls übliche pharmakologisch verträgliche Hilfsstoffe und bzw. oder Trägerstoffe enthalten. Beispiele für geeignete feste Trägerstoffe sind Maisstärke, Calciumsulfatdihydrat und Milchzucker.

Die Arzneimittel können entweder feste oder flüssige Präparate zur oralen Verabfolgung, Suppositorien, Injektionspräparate oder Inhalationspräparate sein. Präparate zur oralen Verabreichung liegen vorzugsweise in Form von Tabletten vor, die nach üblichen Verfahren hergestellt und gegebenenfalls dragiert sein können. Es kommen auch lösliche Sublingualtabletten in Frage.

Injektionspräparate können mit physiologisch verträglichen Trägerstoffen und Hilfsstoffen als Lösungen, Suspensionen oder als Trockenpräparate hergestellt werden, die vor der Verwendung mit dem Verdünnungsmittel versetzt werden. Inhalationspräparate werden vorzugsweise in Form von Aerosolspray-Präparaten hergestellt.

Die Beispiele erläutern die Erfindung.

Beispiel 1

Spaltung von dl-5-(2-Benzyl-tert.-butylamino-1-hydroxyäthyl)-2-benzyloxybenzoesäuremethylester und Umwandlung in die (+)- und (−)-Isomeren von α¹-tert.-Butylaminomethyl-4-hydroxy-m-xylylen-α¹,α³-diol

a) (−)-5-(2-Benzyl-tert.-butylamino-1-hydroxyäthyl)-2-benzyloxybenzoesäuremethylester

Eine Lösung von 30 g der racemischen Base — hergestellt durch Kondensation von 2-Benzyloxy-5-bromacetylbenzoesäuremethylester (vgl. J. Med. Chem., Bd. 13 [1970], S. 674) mit tert.-Butylbenzylamin in Methyläthylketon und Reduktion des erhaltenen Produktes mit Natriumborhydrid in Äthanol nach dem in der FR-Patentschrift 15 57 677 beschriebenen Verfahren — und 25,6 g (+)-O,O-Di-p-toluylweinsäure in 350 ml Äthylacetat wird auf 70°C erwärmt und anschließend langsam auf Raumtemperatur abkühlen gelassen. Das auskristallisierte Salz wird abfiltriert und getrocknet. Ausbeute 27 g vom F 130,0°C; $[\alpha]_D^{25}$ = +49° (c = 1; CH_3OH). Nach dreimaliger Umkristallisation aus Äthylacetat erhält man die Verbindung mit konstantem Schmelzpunkt von 142,5°C und konstantem Drehwert $[\alpha]_D^{25}$ = +47°C (c = 1,2; CH_3OH).

10 g des erhaltenen Salzes in Äthylacetat werden mit wäßriger Natriumbicarbonatlösung behandelt. Die freie Base geht in die Äthylacetatphase über während die Toluylweinsäure in die wäßrige Lösung übergeht. Die Äthylacetatlösung wird eingedampft und der Rückstand aus Petroläther (Siedebereich 40 bis 60°C) umkristallisiert. Man erhält 3 g der freien Base in farblosen Nadeln vom F 87,0°C; $[\alpha]_D^{25}$ = −18,4° (c = 0,38; CH_3OH).

b) (+)-5-(2-Benzyl-tert.-butylamino-1-hydroxyäthyl)-2-benzyloxybenzoesäuremethylester

Diese Verbindung wird in ähnlicher Weise wie

vorstehend beschrieben mit (−)-O,O-Di-p-toluylweinsäure erhalten. Es werden 30 g der racemischen Base und 25,6 g (−)-O,O-Di-p-toluylweinsäure in 350 ml Äthylacetat zur Umsetzung gebracht. Ausbeute 27 g des Salzes vom F 134 bis 135°C; $[\alpha]_D^{20} = -48°$ (c = 1; CH_3OH). Nach dreimaliger Umkristallisation aus Äthylacetat hat das Salz einen konstanten Schmelzpunkt von 141,5°C und einen konstanten Drehwert $[\alpha]_D^{20}$ von −47° (c = 1,5; CH_3OH).

11 g des erhaltenen Salzes in Äthylacetat werden mit wäßriger Natriumbicarbonatlösung behandelt. Die in Freiheit gesetzte Base geht in die Äthylacetatphase über, während die (−)-O,O-Di-p-toluylweinsäure in die wäßrige Lösung übergeht. Die Äthylacetatlösung wird eingedampft und der Rückstand aus Petroläther vom Siedebereich 40 bis 60°C umkristallisiert. Man erhält 4,5 g der freien Base vom F 87,0°C; $[\alpha]_D^{20} = +18,3°$ (c = 0,35; CH_3OH).

c) (+)-α¹-tert.-Butylaminomethyl-4-hydroxy-m-xylylen-α¹,α³-diol-acetat

Eine Lösung von 2,5 g (−)-5-(2-Benzyl-tert.-butylamino-1-hydroxyäthyl)-2-benzyloxybenzoesäuremethylester in wasserfreiem Tetrahydrofuran wird innerhalb eines Zeitraumes von 5 Minuten in eine gerührte Lösung von 0,5 g Lithiumaluminiumhydrid in 50 ml wasserfreiem Tetrahydrofuran eingetropft. Das Gemisch wird unter Rückfluß erhitzt und abkühlen gelassen. Anschließend wird nicht umgesetztes Lithiumaluminiumhydrid mit Wasser zersetzt und das Gemisch mit Äther extrahiert. Nach dem Eindampfen des Ätherextraktes hinterbleiben 2,1 g α¹-Benzyl-tert.-butylaminomethyl-4-benzyloxy-m-xylylen-α¹,α³-diol als farbloses Öl. Das farblose Öl wird in 50 ml Äthylacetat in Gegenwart von 0,7 g 10prozentigem Palladium-auf-Holzkohle hydriert, bis die Wasserstoffaufnahme aufhört. Nach dem Abfiltrieren des Katalysators und Verdampfen des Lösungsmittels hinterbleibt (+)-α¹-tert.-Butylaminomethyl-4-hydroxy-m-xylylen-α¹,α³-diol als farbloses Produkt; $[\alpha]_D^{20} = +25°$ (c = 0,4; CH_3OH). Die freie Base wird in das kristalline Acetat umgewandelt, das nach Umkristallisation aus einer Mischung von Methanol und Äther bei 143,0°C schmilzt; $[\alpha]_D^{20} = +36,9°$ (c = 0,23; CH_3OH). Dieses Salz kristallisiert mit 1 Mol Methanol.

d) (−)-α¹-tert.-Butylaminomethyl-4-hydroxy-m-xylylen-α¹,α³-diol-acetat

Auf die in (c) beschriebene Weise wird der (+)-5-(2-Benzyl-tert.-butylamino-1-hydroxyäthyl)-2-benzyloxybenzoesäuremethylester mit Lithiumaluminiumhydrid reduziert und anschließend katalytisch entbenzyliert. Man erhält das (−)-α¹-tert.-Butylaminomethyl-4-hydroxy-m-xylylen-α¹,α³-diol; $[\alpha]_D^{20} = -26°$ (c = 0,36; CH_3OH). Die freie Base wird in das Acetat überführt und aus Methanol umkristallisiert. Das Acetat kristallisiert mit 1 Mol Methanol und schmilzt bei 143,9°C; $[\alpha]_D^{20} = -36,9°$ (c = 0,27; CH_3OH).

Die nachstehenden Beispiele erläutern die Herstellung von Arzneipräparaten aus den optischen Enantiomeren oder ihren Salzen, die gemäß Beispiel 1 hergestellt wurden.

Beispiel 2

Zur Herstellung von Tabletten werden die nachstehend aufgeführten Bestandteile in den angegebenen Mengen verwendet.

Rezeptur	1 mg Tablette	10 000 Tabletten
Arzneistoff	1,2 mg	12,0 g
Calciumsulfat-dihydrat	88,2 mg	882,0 g
Maisstärke	24,0 mg	240,0 g
Modifizierte Stärke	6,0 mg	60,0 g
Magnesiumstearat	0,6 mg	6,0 g
	120,0 mg	1200,0 g

Die Tabletten werden folgendermaßen hergestellt:

1. Sämtliche Bestandteile, mit Ausnahme des Magnesiumstearats, werden miteinander vermischt, das Pulvergemisch wird mit Wasser granuliert und die feuchte Masse durch ein Sieb der lichten Maschenweite 1,2 mm passiert;
2. Das feuchte Granulat wird getrocknet und anschließend durch ein Sieb der lichten Maschenweite 0,841 mm passiert;
3. Das getrocknete Granulat und das Magnesiumstearat werden hierauf miteinander vermischt und in einer Tablettiermaschine mit üblichen konkaven Stempeln mit einem Durchmesser von 6,35 mm zu Tabletten verpreßt.

Beispiel 3

Zur Herstellung eines Aerosolpräparates werden die nachstehend genannten Bestandteile miteinander vermischt:

Rezeptur	100 µg Dosis
Arzneistoff	100 µg
Ölsäure	10 µg
Dichlordifluormethan	61 mg
Trichlorfluormethan	24 mg

Der Arzneistoff, die Ölsäure und ein Teil des Trichlorfluormethans werden miteinander vermischt. Anschließend wird die erhaltene Suspension mit dem restlichen Trichlorfluormethan verdünnt und in eine Sprühdose abgefüllt, die mit einem Dosierventil verschlossen wird. Hierauf wird in die Sprühdose Dichlordifluormethan aufgepreßt.

Beispiel 4

Zur Herstellung eines Aerosolpräparates werden die nachstehend genannten Verbindungen miteinander vermischt:

Rezeptur	100 µg Dosis
Arzneistoff	120 µg
Sorbittrioleat	120 µg
Dichlordifluormethan	61 mg
Trichlorfluormethan	24 mg

Der Arzneistoff, das Sorbittrioleat und ein Teil des Trichlorfluormethans werden miteinander vermischt. Hierauf wird die erhaltene Suspension mit dem restlichen Trichlorfluormethan verdünnt und in der erforderlichen Menge in eine Sprühdose abgefüllt, die mit einem Dosierventil versehen wird. Danach wird in die Sprühdose Dichlordifluormethan aufgepreßt.

Beispiel 5

Zur Herstellung eines Aerosolpräparates werden die nachstehend genannten Bestandteile verwendet:

Rezeptur	100 µg Dosis
Arzneistoff	120 µg
2-Dimethylaminoäthanol	26,6 µg
Ölsäure	93,4 µg
Dichlordifluormethan	61 mg
Trichlorfluormethan	24 mg

Der Arzneistoff, die Ölsäure, das 2-Dimethylaminoäthanol und ein Teil des Trichlorfluormethans werden miteinander vermischt. Hierauf wird die erhaltene Suspension mit dem restlichen Trichlorfluormethan verdünnt und die erforderliche Menge in eine Sprühdose abgefüllt, die mit einem Dosierventil verschlossen wird. Danach wird in die Sprühdose Dichlordifluormethan aufgepreßt.

PATENT APPLICATION FEE DETERMINATION RECORD

Effective October 1, 1995

Application or Docket Number: 09/16074

CLAIMS AS FILED - PART I

	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA
FOR		
BASIC FEE		
TOTAL CLAIMS	12 minus 20 =	*
INDEPENDENT CLAIMS	3 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		

SMALL ENTITY RATE	SMALL ENTITY FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY FEE
	375.00	OR		750.00
x$11=		OR	x$22=	
x39=		OR	x78=	
+125=		OR	+250=	
TOTAL	375	OR	TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2

CLAIMS AS AMENDED - PART II

AMENDMENT A	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
x$11=		OR	x$22=	
x39=		OR	x78=	
+125=		OR	+250=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
x$11=		OR	x$22=	
x39=		OR	x78=	
+125=		OR	+250=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
x$11=		OR	x$22=	
x39=		OR	x78=	
+125=		OR	+250=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

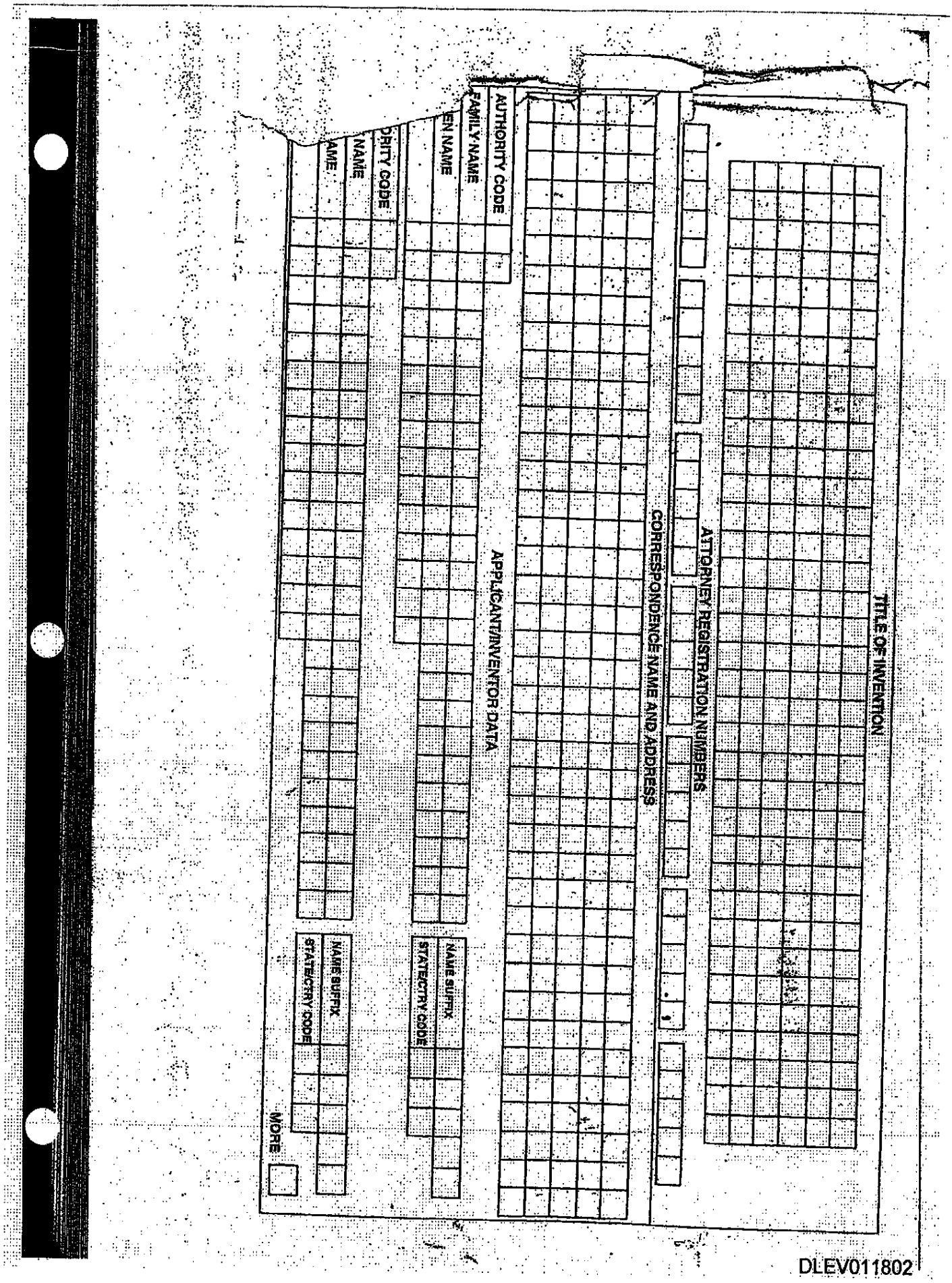
FORM PTO-875 (Rev. 10/95)

Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

DLEV011800

PTO 1556
U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office
PAGE DATA ENTRY CODING SHEET
APPLICATION NUMBER
TOTAL CLAIMS
INDEPENDENT CLAIMS
TYPE APPL
SMALL ENTITY?
FILING DATE
MONTH
DAY
YEAR
FILING FEE
FOREIGN LICENSE
SPECIAL HANDLING
1ST EXAMINER
2ND EXAMINER
GROUP ART UNIT
CLASS
ATTORNEY DOCKET NUMBER
SHEETS OF DRAWING
DATE
CONTINUITY DATA
CONT CODE
STATUS CODE
PARENT APPLICATION SERIAL NUMBER
PCT APPLICATION SERIAL NUMBER
PARENT PATENT NUMBER
PARENT FILING DATE
PCT/FOREIGN APPLICATION DATA
FOREIGN PRIORITY CLAIMED
COUNTRY CODE
PCT/FOREIGN APPLICATION SERIAL NUMBER
FOREIGN FILING DATE

DLEV011801


TITLE OF INVENTION
ATTORNEY REGISTRATION NUMBERS
CORRESPONDENCE NAME AND ADDRESS
APPLICANT/INVENTOR DATA
AUTHORITY CODE
FAMILY NAME
NAME SUFFIX
STATE/CTRY CODE
MORE
DLEV011802

BAR CODE LABEL

U.S. PATENT APPLICATION

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT
08/335,480	11/07/94 RULE 60	514	1205

APPLICANT

TIMOTHY J. BARBERICH, CONCORD, MA; JAMES W. YOUNG, STILL RIVER, MA.

CONTINUING DATA*******************
VERIFIED THIS APPLN IS A CON OF 08/163,581 12/07/93 PAT 5,362,755
WHICH IS A CON OF 07/896,725 06/09/92
WHICH IS A CON OF 07/461,262 01/05/90

FOREIGN/PCT APPLICATIONS**********
VERIFIED

FOREIGN FILING LICENSE GRANTED 01/20/95 ***** SMALL ENTITY *****

STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS	FILING FEE RECEIVED	ATTORNEY DOCKET NO.
MA	0	12	3	$365.00	0701.027C

ADDRESS

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TITLE

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

TITLE OF INVENTION

This is to certify that annexed hereto is a true copy from the records of the United States Patent and Trademark Office of the application which is identified above.

By authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

Date Certifying Officer

US005760090A

United States Patent [19]

[11] Patent Number: 5,760,090

[45] Date of Patent: *Jun. 2, 1998

Barberich et al.

[54] METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(−) ALBUTEROL

[75] Inventors: Timothy J. Barberich, Concord; James W. Young, Still River, both of Mass.

[73] Assignee: Sepracor, Inc., Marlborough, Mass.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,362,755.

[21] Appl. No.: 691,684

[22] Filed: Aug. 15, 1996

Related U.S. Application Data

[63] Continuation of Ser. No. 335,480, Nov. 7, 1994, Pat. No. 5,547,994, which is a continuation of Ser. No. 163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] Int. Cl.[6] A61K 31/135
[52] U.S. Cl. 514/649; 514/826
[58] Field of Search 514/649

[56] References Cited

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Pauwels, "Effect of corticosteroids on the action of sympathomimetics" *Index Medicus* 86:051970.

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Chapman et al. "Racemic mixtures at root of worsening symptoms? Active enantiomers ..." *TIPS* 13, 231–232 (1992).

Muittari et al. "Comparison of acute bronchodilator effects of oral salbutamol, ..." *Chem. Abstr.* 89: 123259m (1978).

Primary Examiner—Raymond Henley, III
Attorney, Agent, or Firm—Heslin & Rothenberg, P.C.

[57] ABSTRACT

The optically pure R(−) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(−) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

9 Claims, No Drawings

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(−) ALBUTEROL

This is a continuation of U.S. application Ser. No. 08/335,480, filed Nov. 7, 1994, now U.S. Pat. No. 5,547,996, which is a continuation of U.S. application Ser. No. 08/163,581 filed Dec. 7, 1993, now U.S. Pat. No. 5,362,755, which is a continuation of U.S. application Ser. No. 07/896,725, filed Jun. 9, 1992, abandoned, which is a continuation of U.S. application Ser. No. 07/461,262, filed Jan. 5, 1990, abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilatory such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the broncho-dilation activity of the R(−) enantiomer of albuterol to provide relief from

bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in effective treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α'[(tert-butylamino) methyl] -4-hydroxy,m-xylene-α, α-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−)-albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or

propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims:

We claim:

1. A method of treating asthma, while reducing side effects associated with the administration of racemic albuterol, comprising administering to an individual suffering from asthma a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method according to claim 1, wherein the albuterol comprises at least 90% by weight of the R(−) isomer and not more than 10% by weight of the S(+) isomer.

3. A method according to claim 1, wherein the albuterol comprises at least 99% by weight of the R(−) isomer and 1% or less by weight of the S(+) isomer.

4. A method according to claim 1, wherein the optically pure R(−) albuterol is administered by inhalation.

5. A method according to claim 4, wherein the optically pure R(−) albuterol is administered in an amount of about 30 μg to about 90 μg.

6. A method according to claim 1, wherein the optically pure R(−) albuterol is administered orally.

7. A method according to claim 6, wherein the optically pure R(−) albuterol is administered in an amount of about 1 mg to about 8 mg.

8. A method according to claim 6, wherein the optically pure R(−) albuterol is administered as a syrup.

9. A method according to claim 7, wherein the optically pure R(−) albuterol is administered as a syrup.

* * * * *

US005547994A

United States Patent [19]

Barberich et al.

[11] Patent Number: 5,547,994

[45] Date of Patent: Aug. 20, 1996

[54] METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

[75] Inventors: Timothy J. Barberich, Concord; James W. Young, Still River, both of Mass.

[73] Assignee: Sepracor, Inc., Marlborough, Mass.

[21] Appl. No.: 335,480

[22] Filed: Nov. 7, 1994

Related U.S. Application Data

[63] Continuation of Ser. No. 163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] Int. Cl.[6] A61K 31/135

[52] U.S. Cl. 514/649; 514/826

[58] Field of Search 514/649, 826

[56] References Cited

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5,362,755 11/1994 Barberich et al. 514/649

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Mishani et al. "Comparison of acute bronchodilator effects of oral salbutamol . . . " *Chem. Abstr.* 89: 123259m (1978).

Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Hoslin & Rothenberg, P.C.

[57] ABSTRACT

The optically pure R(-) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(-) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

6 Claims, No Drawings

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(−) ALBUTEROL

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 08/163,581, filed Dec. 7, 1993 and now U.S. Pat. No. 5,362,755, which was a continuation of application Ser. No. 07/896,725, filed Jun. 9, 1992, now abandoned, which was a continuation of application Ser. No. 07/461,262 filed Jan. 5, 1990, now abandoned.

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The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the bronchodilation activity of the R(−) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1 [(tert-butylamino) methyl] -4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc, or as individual compounds. The components included in a par-

ticular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of treating an acute attack of asthma, while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to an individual suffering from an acute attack of asthma a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method of claim 1 wherein the amount of the R(−) isomer of albuterol is greater than approximately 90% by weight.

3. A method of claim 2 wherein the amount of the R(−) isomer of albuterol is greater than 99% by weight.

4. A method of claim 1 comprising administering to the individual by inhalation from approximately 30 mcg to approximately 90 mcg of the R(−) isomer of albuterol per dose.

5. A method of treating an acute attack of asthma, while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to an individual suffering from an acute attack of asthma a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, and at least one additional drug selected from the group consisting of bronchodilators, antihistamines and analgesics.

6. A method of claim 5 wherein the analgesic is selected from the group consisting of: aspirin, acetaminophen and ibuprofen.

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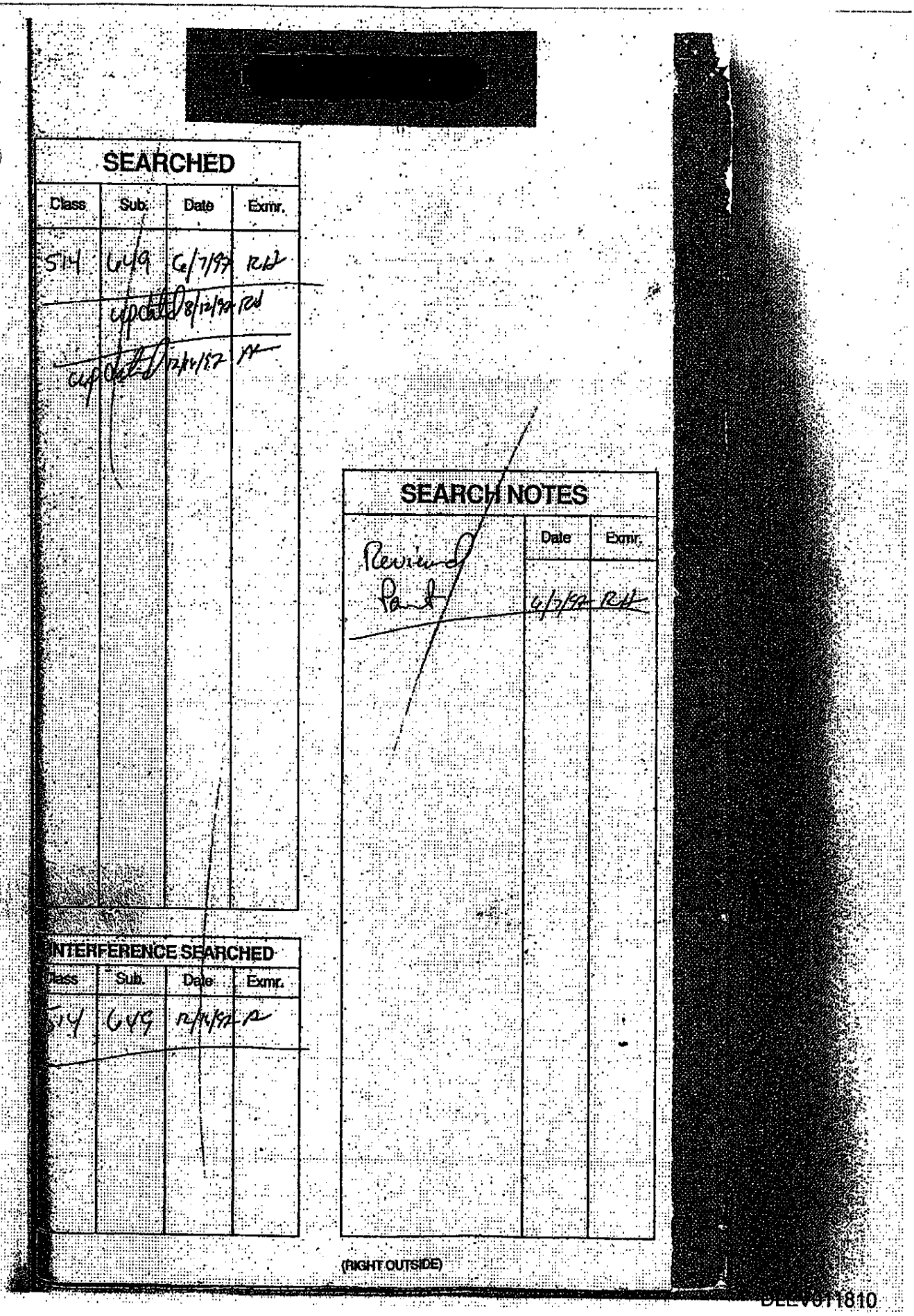

SEARCHED

Class	Sub.	Date	Exmr.
514	649	6/7/97	RLL
	updated	8/12/98	RLL
	updated	12/14/17	AK

SEARCH NOTES

	Date	Exmr.
Reviewed Part	6/7/97	RLL

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.
514	649	12/14/17	AK

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POSITION		ID NO.	DATE
CLASSIFIER			
EXAMINER		308	9/3/96
TYPIST		MB	5/19/97
VERIFIER		211	5/13
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SYMBOLS

✓ ——— Rejected
= ——— Allowed
(Through number) ——— Cancelled
W ——— Withdrawn
I ——— Interference
A ——— Appeal
O ——— Objected

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APPROVED FOR LICENSE

INITIALS

PATENT APPLICATION

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